REMARKS

In order to expedite the prosecution of the present application, Claims 20-23 have been canceled. Newly presented Claims 24 and 25 are directed to preferred embodiments of the present invention. No new matter has been added.

Claims 16-23 have been rejected under 35 USC 112, first paragraph, for, while being enabling for inhibiting malignant tumor progression in mice, not reasonably providing enablement for inhibiting malignant tumor progression in humans. Claims 16-23 have been rejected under 35 USC 103(a) as being unpatentable over Ginoux in view of Postaire et al, Takenaga et al, van Rossen et al and Das et al. Applicants respectfully traverse these grounds of rejection and urge reconsideration in light of the following comments.

The Examiner has taken the position in the rejection of Claims 16-23 under 35 USC 112, first paragraph, that the use of mice models for exhibiting the claimed effects of inhibiting malignant tumor progression is not sufficient to provide enablement for inhibiting malignant tumor progression in humans. As discussed in MPEP § 2164.02, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.

The use of mice models in proving the efficacy of cancer treatment in humans is well known in the art. While the arguments made by the Examiner against the use of mice models in the specification may be valid, the question to be asked is whether the use of mice models for cancer treatment have been accepted in the art as being enabling for cancer treatment in humans. The answer is clearly yes as most of the issued patents directed to the treatment of cancer have used mice

models as have the prior art cited by the Examiner. As such, Applicants respectfully submit that the presently claimed invention clearly is enabled by the present specification and the Board of Appeals would overturn the Examiner's rejection under 35 USC 112, first paragraph, on appeal. Withdrawal of this ground of rejection is respectfully solicited.

The present invention is based on the discovery that the malignant progression of a tumor is inhibited through the oral administration of SOD treated with gliadin, hereinafter referred to as SOD-G. Malignant progression of a cell as a result of genetic changes in a tumor cell toward a more malignant tumor cell is described on page 1, lines 22-27 of the present specification. The malignancy of a tumor is characterized by an autonomous growth in a host, invasiveness, metastasis, rapid growth and/or resistance to anticancer agents.

In the experimental system of the present invention, benign tumor cells are used. One of the characteristics of a benign tumor, generally speaking, is that the tumor cell cannot grow in a host. The benign tumor cell used in the present invention, QR-32, cannot grow in a host by itself as is shown in Tables 1, 2 and 4. However, QR-32 cells can grow in a host when the cell is co-transplanted with a gelatin-sponge as shown in Tables 1, 2 and 4. The presence of the gelatin-sponge with the benign tumor cells produced malignant progression of the benign tumor.

There are two features in the experimental system applied in the present invention with respect to the inhibition of malignant progression of benign tumor cells. The first is the use of benign tumor and biologically inert materials to induce malignant progression and the second is if tumor growth was observed at the site of implantation of the benign tumor, the character of the tumor cells showing the features of malignant progression was examined by histopathologic examination of the growing tumor or, as shown in Tables 1, 2 and 4 in

Experiment B, the evaluation of the metastatic ability of the tumor cell lines established from the arising tumors.

The original benign tumor cells from strain QR-32 did not develop lung metastasis by intravenous injection in normal mice, as shown in column 4 of Table 1, column 7 of Table 2 and column 5 of Table 4. In contrast thereto, tumor cell lines obtained from both groups treated with saline and SOD in Experiment A developed lung metastasis after intravenous injection of the tumor cell lines in Experiment B as shown in Table 4. On the other hand, in contrast to the metastatic malignant progression of saline- and SOD-treated groups, none of the cell lines established from the SOD-G treated group were metastatic. The inhibition of malignant progression is shown in Experiment B by comparing the number of lung metastasis foci between the original tumor cells of QR-32 and those from the established cell lines obtained from the tumor nodules in Experiment A.

Conventional anti-tumor agents are based on selective toxicity. That is, compounds are sought which are harmful to tumor cells and less toxic or benign to normal cells. However, most anti-tumor agents have an adverse effect because a toxic dose for tumor cells also acts as a toxic dose to normal human cells. In contrast to anti-tumor agents, the present invention does not depend on selective toxicity. As discussed in the background of the invention of the present application, the present invention is based on the inhibition of genetic change of DNA through the inhibition of the oxidation of the DNA of benign tumor cells to become tumor cells through DNA oxidation. The inhibition of damage by oxidation of body constituents such as DNA, proteins and lipids has been recommended in that this damage is believed to be the cause of aging and cancer. The prevention of oxidative damage is also good for both tumor treatment as well as the health of the host. The present invention effectively prevents malignant progression of benign tumor cells to metastatic tumor cells through the oral administration of

SOD-G and differs radically from the treatment of traditional anti-tumor agents. As such, the Examiner's discussion with respect to the present invention not being enabled through his rationale utilizing conventional tumor treatment is not well-founded and the presently claimed invention clearly is patentably distinguishable over the prior art cited by the Examiner.

The Ginoux et al reference discloses that a soluble *Cucumis melo* protein extract has a superoxide dismutase enzyme activity and that this protein extract is useful for cosmetic purposes, medical purposes, such as anti-cancer agents for the digestive system and as an antioxidant, in food purposes, such as the replacement of synthetic antioxidants. As previously explained, although this reference discloses that protein extracts containing an elevated superoxide dismutase activity can be used to treat certain cancers of the digestive system, this is only due to the fact that orally administered SOD contacts directly with tumors located in the digestive tract before inactivation of the SOD occurs by proteinases contained in the digestive juices. Nothing in this reference suggests that the inhibition of malignant progression from a benign tumor to a malignant tumor could be accomplished through the administration of SOD-G. In fact, this reference has no disclosure with respect to SOD-G. Therefore, the secondary references cited by the Examiner must supply these teachings in order to present a proper showing of prima facie obviousness under 35 USC 103(a). It is respectfully submitted that the secondary references contain no such teachings.

The Postaire et al reference discloses pharmaceutical compositions that are suitable for orally administering superoxide dismutases which are used in the treatment of inflammatory processes, such as rheumatism and fibrosis, viral processes, such as HIV infection, and toxic conditions associated with the presence of substantial amounts of oxygen, such as central nervous system disorders, ischemia, non-vascular gastrointestinal disorders, eye disorders or control

of the undesirable side affects of anti-cancer treatments. Postaire et al further discloses that superoxide dismutases can be administered with prolamines, such as gliadin. However, like the previously discussed reference, nothing in this reference suggests that the malignant progression of a tumor cell from a benign tumor to a malignant tumor can be prevented through the oral administration of SOD-G. Therefore, this reference adds nothing to the previously discussed reference.

The Takenaga et al reference examines the effect of lecithinized SOD on experimental pulmonary metastasis in mice. However, like the previously discussed references, this reference has no disclosure with respect to the use of benign tumor cells and the prevention of the malignant progression of the benign tumor cells to malignant tumor cells through the oral administration of SOD-G. Therefore, this reference adds nothing to the previously discussed references.

The van Rossen et al reference discloses the diminishing of peritoneal tumor reoccurrence through the scavenging of reactive oxygen species. Like the previously discussed references, this reference is concerned with tumor inhibition and not the prevention of the malignant progression of a benign or dormant tumor to a malignant tumor. Therefore, this reference also adds nothing to the disclosures of the previously discussed references.

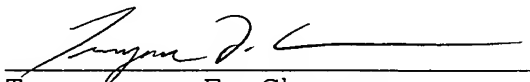
The Das et al reference examines the effect of the consumption of tea on the inhibition of tumor growth and inflammation. According to this reference, SOD was found to be significantly increased in the serum of mice administered tea. This reference discloses that the administration of black and green tea significantly inhibited tumor growth in mice. However, like the previously discussed references, this reference has no disclosure with respect to the oral administration of SOD-G preventing the malignant progression of a benign tumor to a malignant tumor. Therefore, it is respectfully submitted that the references cited by the

Examiner, either singularly or in combination, does not even present a showing of prima facie obviousness under 35 USC 103(a) with respect to the presently claimed invention.

Although, as pointed out above, the references cited by the Examiner do not even present a showing of prima facie obviousness under 35 USC 103(a), Applicants are enclosing herewith a Declaration Under 37 CFR 1.132 which presents additional test data further establishing the unobviousness of the presently claimed invention. In the enclosed Declaration Under 37 CFR 1.132, the oral administration of SOD-G is compared with the oral administration of melon SOD for inhibiting the malignant progression of human colonic adenoma cells. As shown by the results contained in Table 5 of the enclosed Declaration Under 37 CFR 1.132, the oral administration of SOD-G to mice effectively inhibited the malignant progression of human colonic adenoma in the mice while the oral administration of melon SOD had no effect. This is clearly unexpected in light of the disclosure of the references cited by the Examiner and further establishes the unobviousness of the presently claimed invention. Additionally, it should be noted that all of the references cited by the Examiner utilized mice in establishing the efficacy of the cancer treatment protocols.

The Examiner is respectfully requested to reconsider the present application and to pass it to issue.

Respectfully submitted,



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